Recommendations for Use of a Booster Dose of Inactivated Vero Cell Culture-Derived Japanese Encephalitis Vaccine --- Advisory Committee on Immunization Practices, 2011

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Japanese encephalitis (JE) virus, a mosquito-borne flavivirus, is an important cause of encephalitis in Asia with a case fatality rate of 20%--30% and neurologic or psychiatric sequelae in 30%--50% of survivors (1). Travelers to JE-endemic countries and laboratory personnel who work with infectious JE virus are at potential risk for JE virus infection. In 2010, CDC's Advisory Committee on Immunization Practices (ACIP) updated recommendations for prevention of JE. The updated recommendations included information on use of a new inactivated, Vero cell culture--derived JE vaccine (JE-VC [manufactured as Ixiaro]) that was licensed in the United States in 2009. Data on the need for and timing of booster doses with JE-VC were not available when the vaccine was licensed. This report summarizes new data on the persistence of neutralizing antibodies following primary vaccination with JE-VC and the safety and immunogenicity of a booster dose of JE-VC. The report also provides updated guidance to health-care personnel regarding use of a booster dose of JE-VC for U.S. travelers and laboratory personnel. ACIP recommends that if the primary series of JE-VC was administered >1 year previously, a booster dose may be given before potential JE virus exposure.

Background

For most travelers to Asia, the risk for JE is very low but varies based on destination, duration, season, and activities (2). ACIP recommends JE vaccine for travelers who plan to spend a month or longer in JE-endemic areas during the JE virus transmission season. JE vaccine should be considered for short-term travelers (<1 month) if they plan to travel outside of an urban area and have an itinerary or activities that will increase the risk of JE virus exposure. JE vaccine also is recommended for laboratory personnel with a potential for exposure to infectious JE virus (1).

In 2009, the Food and Drug Administration (FDA) licensed JE-VC for use in persons aged ≥17 years. JE-VC is manufactured by Intercell Biomedical (Livingston, United Kingdom) and is distributed in the United States by Novartis Vaccines (Cambridge, Massachusetts). JE-VC is administered in a 2-dose primary series at 0 and 28 days. Another JE vaccine, an inactivated mouse brain--derived vaccine (JE-VAX [JE-MB]), has been licensed in the U.S since 1992. However, JE-MB is no longer being produced and remaining doses expire in May 2011.

Additional JE-VC study data have become available since the vaccine's licensure. The ACIP JE Vaccines Workgroup reviewed JE-VC clinical trial data on the persistence of neutralizing antibodies following primary vaccination with JE-VC and the safety and immunogenicity of a booster dose of JE-VC. These were primarily from published, peer-reviewed studies; however, unpublished data also were considered. FDA approved an update to the prescribing information for JE-VC in September 2010. No previous guidelines have been given on booster doses with JE-VC. At the February 2011 ACIP meeting, the workgroup presented data supporting use of a booster dose and proposed recommendations for a booster dose. ACIP approved the booster dose recommendations at the meeting.

Persistence of protective neutralizing antibodies after primary vaccination with JE-VC

Three clinical trials have provided data on persistence of protective neutralizing antibodies after a primary 2-dose

series of JE-VC. In JE vaccine clinical trials, JE virus neutralizing antibody levels measured by plaque reduction neutralization test (PRNT) can be used as a surrogate for protection. A 50% PRNT ($PRNT_{50}$) titer of ≥10 is accepted as an immunologic correlate of protection from JE in humans (*3*). In a study performed in central Europe (Austria, Germany, and Romania) to evaluate persistence of neutralizing antibodies among subjects who received 2 doses of JE-VC, 95% (172 of 181), 83% (151 of 181), 82% (148 of 181) and 85% (129 of 152) had protective antibodies at 6 months, 12 months, 24 months, and 36 months after receiving the first dose, respectively (Table 1) (*4*--*6*). A study that used similar methods but was performed in western and northern Europe (Germany and Northern Ireland) found that among adults receiving 2 doses of JE-VC, seroprotection rates were 83% (96 of 116) at 6 months, 58% (67 of 116) at 12 months, and 48% (56 of 116) at 24 months after their first vaccination (Table 1) (*7*). The manufacturer suggested that the different seroprotection rates in the two populations may have resulted from differences in prior vaccination against tick-borne encephalitis (TBE) virus, a related flavivirus. An estimated 75% of subjects in the first study might have received prior TBE vaccine compared with none of the subjects in the second study. A higher JE virus neutralizing antibody response after the first dose of JE-VC previously had been found in subjects with preexisting TBE antibodies compared with those without TBE antibodies (*8*). In a third clinical trial, conducted in Austria and Germany, at 15 months after the first dose of a 2-dose JE-VC immunization series, 69% (137 of 198) of subjects had a protective neutralizing antibody titer (Table 1) (*9*).

Safety and immunogenicity of a booster dose of JE-VC

Two clinical trials have provided data on the response to a booster dose of JE-VC. In a study conducted in Austria and Germany, 198 adults aged ≥18 years who had received a 2-dose primary series of JE-VC were administered a booster dose 15 months after the first dose (*9*). The percentage of subjects with a protective neutralizing antibody titer increased from 69% (137 of 198) on Day 0 before the booster dose to 100% (198 of 198) at Day 28 after the booster dose. Protective titers were found in 98% (194 of 197) at 6 months and 98% (191 of 194) at 12 months after the booster dose (Table 2). The geometric mean titer (GMT) before the booster was 23 and increased 40-fold to 900 at Day 28 after the booster dose. GMTs were 487 and 361 at 6 and 12 months after the booster, respectively (Table 2). During the 7 days following the booster dose, local adverse events were reported in subject diaries by 31% (60 of 195) of subjects. The most frequent local reactions were tenderness in 19% (37 of 193) and pain in 13% (25 of 195) (Table 3). Systemic adverse events were reported by 23% (44 of 190) of subjects within 7 days of the booster dose. The most commonly reported systemic reactions were headache in 11% (21 of 194) and fatigue in 10% (18 of 188) (*6*). No serious adverse events were reported during the 28 days following the booster dose.

In a second study, a booster dose administered to 40 subjects who had received primary immunization but no longer had protective neutralizing antibody titers resulted in protective titers in all subjects when the booster was administered at 11 months (n = 16) or 23 months (n = 24) after the first dose (*7*). GMTs at 1 month after the booster increased to 676 and to 2,496 in the groups administered the dose at 11 months and 23 months after the first dose, respectively. Among the 16 subjects who received the booster dose at 11 months, all still had seroprotective titers 13 months later.

Guidelines for use of a booster dose of JE-VC

ACIP recommends that if the primary series of JE-VC was administered >1 year previously, a booster dose may be given before potential JE virus exposure. ACIP recommendations should be consulted for information on prevention of JE and settings in which JE vaccine is recommended, can be considered, or is not recommended (*1*). Data on the response to a booster dose administered >2 years after the primary series of JE-VC are not available. Data on the need for and timing of additional booster doses also are not available.

No data exist on the use of JE-VC as a booster dose after a primary series with inactivated mouse brain-derived JE vaccine (JE-MB [manufactured as JE-Vax]). Adults aged ≥17 years who have received JE-MB previously and require further vaccination against JE virus should receive a 2-dose primary series of JE-VC.

ACIP will review any additional data that are made available. Recommendations will be updated as needed.

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TABLE 1. Number and percentage of subjects with a protective Japanese encephalitis (JE) virus neutralizing antibody titer (≥10) and geometric mean titers (GMT) at month 6, 12, 15, 24, and 36 after dose 1 of a 2-dose primary series of inactivated Vero cell culture--derived JE vaccine (JE-VC [manufactured as Ixiaro])

	Months after the first dose of a 2-dose primary series of JE-VC									
	6 mos		12 mos		15 mos		24 mos		36 mos	
Study site	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Austria, Germany, Romania*†§ [N = 181]	172	(95)	151	(83)	---	---	148	(82)	129	(85)¶
Germany, Northern Ireland** [N = 116]	96	(83)	67	(58)	---	---	56	(48)	---	---
Austria, Germany†† [N = 198]	---	---	---	---	137	(69)	---	---	---	---
	GMT	(95% CI)	GMT	(95% CI)	GMT	(95% CI)	GMT	(95% CI)	GMT	(95% CI)

Austria, Germany, Romania*†§ [N = 181]	84	(71--98)	41	(34--49)	---	---	44	(37--53)	44	(37--53)¶
Germany, Northern Ireland** [N = 116]	47	(37--59)	18	(14--23)	---	---	16	(13--21)	---	---
Austria, Germany†† [N = 198]	---	---	---	---	23	(19--27)	---	---	---	---

TABLE 2. Number and percentage of subjects with a protective Japanese encephalitis virus neutralizing antibody titer (≥10) and the geometric mean titers (GMT) prior to and at day 28, month 6, and month 12 after a booster dose of inactivated Vero cell culture--derived Japanese encephalitis vaccine (JE-VC [manufactured as Ixiaro]) administered 15 months after dose 1 of a 2-dose primary JE-VC series

	Time after administration of the booster dose of JE-VC							
	0 days (N = 198)		28 days (N = 198)		6 months (n = 197)		12 months (n = 194)	
Study site	**No.**	**(%)**	**No**	**(%)**	**No**	**(%)**	**No**	**(%)**
Austria, Germany* [N = 198]	137	(69)	198	(100)	194	(98)	191	(98)
	GMT	**(95% CI)**	**GMT**	**(95% CI)**	**GMT**	**(95% CI)**	**GMT**	**(95% CI)**
	23	(19--27)	900	(742--1091)	487	(391--608)	361	(295--444)

TABLE 3. Number and percentage of local and systemic adverse events occurring within 7 days after a booster dose of inactivated Vero cell culture--derived Japanese encephalitis vaccine (JE-VC [manufactured as Ixiaro]) administered 15 months after dose 1 of a 2-dose primary JE-VC series

Adverse events	No./Total subjects	(%)
Local adverse events		
Tenderness	37/193	(19)
Pain	25/195	(13)
Induration	18/194	(9)
Erythema	12/193	(6)
Edema	4/194	(2)
Any	60/195	(31)
Systemic adverse events		
Headache	21/194	(11)
Fatigue	18/188	(10)
Myalgia	13/194	(7)
Fever	8/195	(4)
Any	44/190	(23)